REMARKS

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of one month of the period for response to the outstanding Office Action on this case. We enclose our cheque in the amount of the prescribed fees for a Small Entity. A Small Entity Declaration is of record in this file.

The Examiner indicated that this application has been filed with informal drawings, which are acceptable for examination purposes. However, it is noted that the only objection made to the drawings is that no Petition has been submitted for the acceptance of photographs in this case. The photographic drawings were filed during the International Phase of this filing. In order to deal with the matter raised in the PTO-948, submitted herewith is a Petition under 37 C.F.R. 1.84(b) for acceptance of photographs in this case.

The Examiner has rejected claims 8 to 15 under 35 U.S.C. 103 as being unpatentable over Moorhead, Chvapil and Raisfield, taken in view of University of Texas WO 91/10427.

Claim 8 of this application has been amended in order to define the invention in more precise terms and in a manner, it is submitted, which clearly distinguishes the present invention from the prior art cited by the Examiner. In particular, claim 8 defines a method of treating or preventing hypertrophic scar tissue in humans. The present invention is directed to the treatment of this specific condition in humans and involves applying to extracellular wound scar tissue in human skin an effective amount of a non-toxic amine compound having a free amino group. Such non-toxic amine compound is a transglutaminase inhibitor which is selective for inhibiting Type III collagen isopeptide cross-linking. The compound also may be a pharmaceutically-acceptable acid addition salt thereof. The amine compound is provided in the form of a composition with a pharmaceutically-acceptable carrier or diluent and formulated for topical application to the extracellular wound. It is submitted that the specification provides clear basis for the addition of the

language of claim 8. The specification clearly describes the use of amine compounds, including putrescine. The specification describes the clinical treatment of extracellular wound scar tissue in human skin. It is indicated that the transglutaminase inhibitor should be selective for inhibiting Type III collagen isopeptide cross-linking. On page 2 and in the case studies, there is described the topical application of the composition to the wound site.

New claim 16 reciting the further step of occluding the wound with a dressing finds basis on page 2 of the specification.

The present invention is concerned with the use of certain amines, preferably putrescine, as claimed in claim 14, topically administered, to prevent or treat hypertrophic scar tissue in human skin through the mechanism of inhibition of the action of tissue transglutaminase. It is submitted that the role of tissue transglutaminase in the formation of hypertrophic scar tissue is not obvious.

Amines of various types have been used throughout the scientific literature to inhibit various enzymes in various biological systems. For example, monoamines and diamines have been used to inhibit lysyl oxidase important in hydroxy lysine production and collagen biosynthesis, as described in the Kagan et al reference cited by the Examiner, but not relied on. This material has had drastic and well-documented clinical toxicity due to generalized collagen inhibition and wound breakdown. Similarly, Moorhead and Chvapil relied on by the Examiner, disclose the use of lysyl oxidase inhibitors of monoamine and diamine types in fibriotic condition treatment. In particular, Moorhead claims the use of beta-aminopropionitrile for inhibiting collagen cross-linking. This reference contains no disclosure or discussion of hypertrophic scar or tissue transglutaminase. The primary clinical application described is in the treatment of ocular injury. The reference is very specific in addressing the role of the inhibitors to inhibit lysyl oxidase, saying nothing

about the role of transglutaminase. The reference, therefore, discloses the use of diamines, but only in the context of lysyl oxidase inhibition and for ocular conditions.

The Chvapil reference claims the use of topical and locally-infused beta-aminopropionitrile for reducing the extent of collagen cross-linking at a wound site. The reference teaches the inhibition of lysyl oxidase which deaminates the amino group of lysine and collagen. The reference contains no mention or discussion of transglutaminase inhibition, but rather discusses collagen cross-linking inhibition extensively.

The Raisfield reference, cited by the Examiner, discloses the use of various amines for wound healing promotion and makes no mention of transglutaminase or of collagen formation inhibition. It is noted that hypertrophic scar tissue is a problem of excessive healing. Raisfield teaches that epithelial growth regulating agents of promoters and inhibitors of unknown function can be used in the treatment of disorders. A variety of scientific publications have noted the ability of polyamines to stimulate tissue proliferation. However, the specific inhibition of tissue transglutaminase in order to prevent or ameliorate hypertrophic scarring is not dealt with, discussed or even hinted at in any such prior art, including the references relied on by the Examiner.

To the extent that any of the primary references that the Examiner has cited discloses specific compounds, the use and the treatments described therein, none of these references discloses the possibility of the utilization of putrescine as claimed in claim 14.

While the University of Texas reference (also the Kapil et al reference cited, but not applied by the Examiner), discloses the use of putrescine but for the inactivation and killing of nematodes, this is a quite different use for the putrescine than use in hypertrophic scar therapy in humans, in accordance with the present invention. The human hypertrophic scar produces too much collagen Type III isopeptide cross-link

and this is inhibited, in accordance with the present invention by the use of certain polyamines, such as putrescine in low local concentrations. The invention also includes other polyamines which have an inhibitory effect on tissue transglutaminase and decreased production of Type III collagen isopeptide cross-linking. It is inhibition of this specific enzyme that has such beneficial and clinical effects topically on hypertrophic scar, as demonstrated by the results of the clinical studies outlined in the specification.

Accordingly, it is submitted that the references that are cited by the Examiner neither disclose or suggest the present invention as defined in the amended claims. The prior art is wholly silent as to the treatment of hypertrophic scar tissue and how such scar may be treated. The art is clearly silent as to the utilization of selected polyamines, particularly putrescine topically applied to extracellular wound scar tissue in human skin, as required in the present invention. The materials used in the present invention must be a transglutaminase inhibitor which is selective for inhibiting Type III collagen isopeptide cross-linking.

Accordingly, it is submitted that claims 8 to 15 and newly submitted claim 16 are patentable over the art and the rejection thereof under 35 U.S.C. 103 as being unpatentable over Moorhead, Chvapil and Raisfield taken in view of the University of Texas should be withdrawn.

It is believed that this application now is in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,

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